FATAL *LISTERIA MONOCYTOGENES* MENINGITIS IN A CHILD AGED 3 MONTHS

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Listeria infections are common amongst animals, but do not often occur in man.

The case reported here was of a boy aged 3 months, the youngest of three children, who had a birth weight of 6 lb. 12 oz. following an uncomplicated pregnancy. No abnormality was detected until one week before admission to hospital, when he became fretful at night, screaming persistently, followed by increasing anorexia and apathy. There was evidence of slight respiratory infection with cough, "snuffles," and feverishness. No skin rashes were observed. He had a major convulsion the night before admission.

On admission on August 8, 1956, he had a temperature of 103° F. and was moderately dehydrated. There was a mucoid discharge from both nostrils. No moist sounds were heard in the chest. The anterior fontanelle was tense and bulging and there was some neck stiffness. Kernig's sign was positive on both sides.

Direct examination of a specimen of cerebrospinal fluid taken on admission showed that numerous polymorph leucocytes were present, but no organisms were seen in a film from the centrifuged deposit. Culture yielded a scanty growth of a small Gram-positive bacillus; this was thought to be a "diphtheroid" organism, and on account of the very small number of colonies was regarded as a contaminant. Blood culture at this stage was negative.

The child was treated as follows for nine days: intrathecal penicillin, 10,000 units daily for three days; intramuscular penicillin (soluble), 500,000 units at once, followed by 200,000 units six hourly for five days, and distaquaine penicillin, 150,000 units daily for a further four days; sulphadimidine 1 g. at once followed by 0.25 g. six hourly for nine days. On the third day of treatment a second specimen of cerebrospinal fluid was examined and found to contain polymorph leucocytes; there was no growth on culture. A small ulcer from which *Proteus* was the only organism isolated developed on the left buttock at the site of the first penicillin injection.

On admission the white cell count was 16,000 cells per c.mm. (88% polymorphs, 11% lymphocytes, and 1% monocytes). Five days later there were 8,800 leucocytes (67% polymorphs, 2% eosinophils, 30% lymphocytes, and 1% monocytes). The temperature fell to normal and recovery was apparently complete.

On August 23, 1956, the fever recurred. He was treated with soluble penicillin, 250,000 units six hourly, and sulphadimidine, 0.5 g. six hourly for three days, and subsequently with chloramphenicol, 100 mg. six hourly, without response. Signs of meningitis reappeared and successive lumbar punctures at this stage showed the following appearances in the cerebrospinal fluid (centrifuged deposits): August 28, occasional red blood cells only; August 30, a few leucocytes, mainly lymphocytes; August 31, numerous polymorph leucocytes and a few lymphocytes.

From this last specimen a Gram-positive bacillus was isolated similar in all respects to that cultured from the cerebrospinal fluid on admission. A blood culture taken on August 28 was contaminated, but similar Gram-positive bacilli were found in the mixed growth obtained.

The organism was provisionally identified as *Listeria monocytogenes* and the treatment was changed to intramuscular streptomycin, 250 mg. b.d., and oral erythromycin, 70 mg. six hourly, in accordance with the sensitivity findings (see bacteriological data). The treatment was, however, ineffective and the child died on September 5, 1956.

During the last few days of life specimens of cerebrospinal fluid were examined daily and showed a marked polymorphonuclear reaction with occasional lymphocytes only; on each occasion a heavy growth of *List. monocytogenes* was obtained.

In view of these findings the family history is of particular interest. Both parents were healthy though the mother had been blind since birth. The father worked as a soil analyst, but had noted nothing abnormal either in his work routine or his personal health at the time of his son's illness. During the first week of the child's illness the second child had a mild respiratory infection while the eldest remained well. There are no domestic pets in the family, and the standard of hygiene in the home was excellent.

Necropsy

The post-mortem findings were as follows:

The body was that of a well-nourished male child aged about 3 months. Small, roughly circular red macules were present in the skin over the buttocks and groin. A single small ulcer, about

1 cm. in diameter, having a grey firm base and clean-cut edges, was on the outer aspect of the left buttock.

The brain and spinal cord were everywhere covered by purulent exudate. Over the superior and anterior aspects of both frontal lobes, the inferior aspect of both temporal lobes, and over the base of the brain, the exudate was yellow and of the consistency of thick cream; elsewhere over the brain and spinal cord it was more translucent and gelatinous with discrete small purulent nodules measuring up to 0.3 cm. diameter scattered throughout.

No pus was seen in either middle ear cavity. The heart, lungs, liver, kidneys, spleen, and other viscera and organs showed no important macroscopic abnormality. Swabs for culture of organisms were taken at necropsy from both middle ear cavities, brain, and spleen.

Brain and Spinal Cord.—The subarachnoid space was filled with chronic purulent inflammatory exudate which had spread along the perivascular spaces into the depths of the sulci. The grey matter of the underlying brain was oedematous and in it were occasional small superficial abscesses. The histological appearances of the exudate were indistinguishable from those seen in any other purulent meningitis. Similar changes were seen in the spinal cord. Sections stained with Gram's method showed cocco-bacillary organisms morphologically indistinguishable from *Listeria monocytogenes* (Fig. 1); they appeared to be both extracellular and intracellular, and had variable staining properties.

Spleen and Lymph Nodes.—The general architecture was preserved, but Malpighian bodies and lymphoid follicles were small and composed entirely of deeply-staining small lymphocytes. There was moderate generalized fibrosis throughout the pulp, which in the spleen was moderately congested and contained numerous macrophages. Polymorphonuclear leucocytes were not present, and appearances were those of chronic inflammation with fibrosis.

Sections from the heart, lungs, liver, pancreas, kidneys, and adrenals showed no important abnormality.

Gram-staining of sections other than those of brain and spinal cord failed to reveal any organisms.

Bacteriology

The characteristics of the *Listeria* isolated from this case were as follows:

The organism was a small Gram-positive but

FIG. 1.—Gram stain $\times 960$ to show *Listeria* organisms in the meningeal exudate.

easily decolorized bacillus occurring singly or in pairs with occasional short chains only.

After overnight cultivation in broth at 37° C. the organism was non-motile, but when grown at 22° C. it showed a vigorous "tumbling" motility.

Growth in the form of small, translucent, smooth colonies was good at 37° C. and slower at 4° C., on ordinary nutrient agar. Growth also occurred on McLeod's tellurite agar, on McConkey's medium, and in 6% sodium chloride broth. On 5% fresh horse blood agar colonies were surrounded by a narrow zone of haemolysis. The catalase test was strongly positive and the oxidase test was negative. There was no liquefaction of gelatin or of Loeffler's serum.

Biochemical Tests.—The methyl-red and Voges-Proskauer tests were positive, there was no growth in citrate medium, and no H_2S or indole was produced.

The organism fermented, with the production of acid but not gas, aesculin, glucose, lactose, laevulose, maltose, mannose, rhamnose, salicin, sucrose, and trehalose, and failed to ferment arabinose, dulcitol, galactose, inositol, inulin, mannitol, raffinose, sorbitol, and xylose.

Conjunctival Test.—Confirmation that the organism was a *Listeria* was obtained by instilling two drops of an overnight broth culture into the

FIG. 2.—Conjunctival test in guinea-pig to show marked corneal opacity.

conjunctival sac of a guinea-pig. An intense purulent conjunctivitis was present after 48 hours (from which a pure and heavy growth of *Listeria* was obtained), but this quickly resolved leaving after five days a marked corneal opacity (Fig. 2). This gradually disappeared and after three weeks the eye appeared normal. It was found, as reported by Julianelle (1941), that the eye subsequently resisted reinfection. This immunity did not, however, extend to the contralateral eye in which a similar reaction could still be demonstrated.

Serology.—The organism was sent to Dr. H. Seeliger, of Bonn, for serological typing, and he reported that it belonged to serotype 4b.

The organism was sensitive to streptomycin, erythromycin, and oleandomycin, weakly sensitive to achromycin, aureomycin, sulphadiazine, sulphamylamide, and sulphadimidine, and resistant to terramycin, chloramphenicol, novobiocin, and penicillin.

Discussion

List. monocytogenes is an uncommon cause of meningitis in man. Seven cases have now been reported in the British literature (Gibson, 1935; Wright and Macgregor, 1939; Barrow and Pugh, 1957; Edmunds, Nicholson, and Douglas, 1957; Mair, Mair, Stirk, and Reid, 1957). In a review of the world literature, Finegold, Bradley, Campbell, and Greenberg (1954) listed 26 cases certainly and 11 cases possibly due to *List. monocytogenes* and described a further two cases of their own. Recently, however, further cases have

been reported from Germany (Eck, 1957) and the U.S.A. (Dedrick, 1957), and the disease may, in fact, be more common than has been generally supposed.

The disease usually presents as an acute meningitis and responsibility for the precise diagnosis rests with the pathologist. Examination of the cerebrospinal fluid reveals a marked polymorphonuclear reaction (the infection is not usually associated with a monocytic response in man) and in many cases small bacilli. Because the organism is easily overdecolorized it may appear to be Gram-negative and at this stage may be mistaken for *Haemophilus influenzae*. On culture, however, the ability of the organism to grow abundantly on simple nutrient agar eliminates this possibility.

Mathieu, Young, Mennillo, and Sherwood (1956) suggested that the colonial and morphological appearances of *List. monocytogenes* might lead to the organism being regarded as a streptococcus or a diphtheroid contaminant. The latter possibility is much the more likely and further tests are necessary to identify the organism. The most significant of these are (a) the motility test, when, if the organism is grown in broth at 22° C., a vigorous "tumbling" motility is observed; (b) growth in 6% salt broth, when the organism grows readily in a fluid medium in the presence of 6% NaCl; (c) a conjunctival test, when a typical conjunctivitis and subsequent keratitis occurs after instillation of a broth culture of the organism into the conjunctival sac of guinea-pig or rabbit.

The findings in the central nervous system in this child, as in the fatal cases reported by Gibson (1935), Burn (1936), Wright and Macgregor (1939), and others (see review by Finegold *et al.*, 1954) are those of a non-specific purulent meningitis. Lesions in the liver, such as have been reported by Wright and Macgregor, are absent. Fibrosis of the splenic pulp has not been reported in any of the fatal cases reviewed by Finegold *et al.*; it is probably the end-result of chronic inflammation and is presumably due to *Listeria* infection, though no organisms can be demonstrated in the sections.

The source of *Listeria* infection in human cases is rarely discovered. There is no evidence that the disease is transmitted directly from animals, and the consensus of opinion is that in babies the most likely source of infection is the maternal genito-urinary tract. The high proportion of neonates amongst cases of *List. monocytogenes*

meningitis appears to support this view (Girard and Gavin, 1957). The case reported by Barrow and Pugh (1957) was a premature baby 12 days old, where a "diphtheroid" organism, not precisely identified, had been recovered previously from the mother's urine. It is interesting to note that the child was delivered by Caesarean section, so that transmission of infection from the mother, if it occurred, was probably *in utero*. An investigation into the frequency with which *List. monocytogenes* occurs in the female genito-urinary tract, especially during pregnancy, might throw some light on the origin of meningitis due to this organism.

Summary

Clinical, bacteriological, and histological findings from a fatal case of *Listerella monocytogenes* meningitis are reported.

Responsibility for the diagnosis of this disease rests with the pathologist, and a comment is made on the most useful tests to establish the identity of organisms.

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